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Summary of the International Symposium on Childhood Non-Rhabdomyosarcoma Soft-Tissue Sarcomas, Padua, Italy, February 10–12, 1994

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INTRODUCTION

The International Symposium on Childhood Non-Rhabdomyosarcoma Soft-Tissue Sarcomas was held on February 10–12, 1994 in Padua, Italy under the leadership of Dr. Modesto Carli. The welcome and opening remarks were given by our host, Dr. Carli.

A. Pathology and Tumor Biology were the topics of the first session, chaired by Drs. Dieter Harms (Kiel, Germany) and William Newton (Columbus, OH).
   1. V. Ninfo (Padua, Italy) reviewed the classic pathologic varieties of non-rhabdomyosarcomatous (non-RMS) soft-tissue sarcomas in childhood. Although many unusual types occur, the most frequent are extraosseous Ewing's (EOE) sarcoma and peripheral neuroectodermal tumor (PNET), malignant peripheral nerve sheath tumor, synovial sarcoma, and fibrosarcoma. These tumors occur primarily in the extremities, on the trunk, in the abdominal-retroperitoneal region, and in the head and neck.
   2. P.F. Ambros (Vienna, Austria) reviewed data regarding cytogenetic abnormalities in non-RMS soft-tissue sarcomas in children. These consist primarily of the translocations t(11;22), t(21;22), and others in patients with EOE and osseous Ewing's sarcoma; the translocation t(X;18) in synovial sarcoma; the presence of an additional chromosome 8, 11, 17, and/or 20 in the tumors of infants with fibrosarcoma, and the der 11p in leiomyosarcoma. Dr. Ambros also reviewed the effectiveness of fluorescent in-situ hybridization (FISH) for the diagnosis of these abnormalities.
   3. D. Shapiro (Memphis, TN) reviewed aspects of DNA ploidy analysis in pediatric soft-tissue sarcomas. Dr. Shapiro cited the known associations of tetraploidy with alveolar rhabdomyosarcoma (RMS) and of diploidy or hyperdiploidy with the histologic diagnosis of embryonal RMS. He stated that the DNA content of osteosarcomas and Ewing's sarcomas has been investigated but few other pediatric soft-tissue sarcomas have been so studied. However, the DNA content of soft-tissue Ewing's tumors appears to be similar to that of Ewing's sarcomas in that it is almost exclusively diploid.
   4. R. Azzarelli (Milan, Italy) reviewed soft-tissue sarcomas other than RMS in adults. He stressed the differences in pathologic grade from grade 1 (generally benign) to grade 3 (obviously malignant microscopically) and the propensity among adults for these tumors to recur locally, as opposed to spreading distantly. When distant spread occurs, it is usually to the lungs. The surgeon may be needed for aggressive attack on the local tumor as well as for possibly removing lung metastases.

B. Pathology: Clinical and Therapeutic Aspects were the topics of the morning session on the second day, chaired by Drs. Joern Treuner (Stuttgart, Germany) and Robert Marcus (Gainesville, FL)
   1. D. Harms reviewed EOE and PNET. His data suggest that EOE and PNET are two ends of a spectrum ranging from no obvious neural differentiation to very obvious neural differentiation. Both histochemical and electron microscopic studies are useful in separating these two tumors. Dr. Harms introduced the use of the term *malignant peripheral neuroectodermal tumor* (MPNT) as a preferable name for one of the different kinds of PNETs, to avoid confusion arising from the fact that "P" in PNET can mean *primitive* (as in tumors of the central nervous system) or *peripheral*. The

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classic Ewing's sarcoma has closely packed, small, round cells with round nuclei and periodic acid-Schiff–positive cytoplasm. The atypical Ewing's tumor has more cytologic atypia: The cells are more variable in size and shape, and the nuclei are larger and more polymorphic. Also, the mitotic rate is higher than in classic Ewing's sarcoma. This tumor appears to stand in the middle of the spectrum, with MPNT at the other end from Ewing's. MPNTs have the cytology and histology of atypical Ewing's sarcoma, but rosettes can be seen and usually neural markers can be demonstrated by immunohistochemical studies, such as neuron-specific enolase, protein S-100, or Leu-7. Dense core granules may be seen on electron microscopy. In the Kiel data, patients with MPNT have a worse outlook compared with patients with classic and atypical Ewing's sarcoma.

2. B. Raney (Houston, TX) presented the Intergroup Rhabdomyosarcoma Study experience with 130 cases of EOE sarcoma in childhood. This review indicated that patients with EOE sarcoma are similar to patients with RMS in childhood in their response to chemotherapy and radiation therapy. In 51 patients with localized, gross residual tumors, the addition of doxorubicin to vincristine, actinomycin D, and cyclophosphamide with radiation therapy was not beneficial in 31 patients (62% of whom were alive at 10 years) compared with the results in 20 patients who received the same therapy without doxorubicin (of whom 65% were alive at 10 years, $P = 0.82$).
3. D. Schmidt (Kiel, Germany) discussed the three types of synovial sarcoma. Approximately 60% of the synovial sarcomas reviewed in Kiel are classic biphasic synovial sarcomas. Of the two monophasic variants, the monophasic fibrous variant is more common than the monophasic epithelial type. The outlook for synovial sarcoma is best when the tumors are small and have been surgically removed. The presence of ossification or mast cells in the tumor is prognostically favorable, whereas the outlook is worse if rhabdoid cells are present. The Kiel data show no difference in outcome between the biphasic and the monophasic tumors.
4. Dr. Treuner presented the results of the German CWS-81 and CWS-86 studies for treatment of synovial sarcoma in childhood and adolescence. The data clearly support the use of chemotherapy with doxorubicin, vincristine, actinomycin D, and cyclophosphamide or ifosfamide as the alkylating agent. Forty-one patients were treated (31 grossly resected, 6 with localized, gross residual tumors, and 4 with distant metastases at diagnosis). The disease-free survival at 5 years was 78%, and the overall survival rate at 5 years was 83%. The event-free survival rate was 84–85% in patients without metastases at diagnosis.
5. Dr. Carli then presented the combined experience of the German and Italian Cooperative Study Groups with malignant peripheral nerve sheath tumors. These tumors were defined by conventional light microscopy and positive immunostaining with vimentin and S-100. The most active chemotherapeutic agents were ifosfamide and a combination of VP-16 and cisplatin. In 65 evaluable patients, the 5-year progression-free survival rate was 34% and the 5-year overall survival rate was 49%. Survival expectancy was best in patients whose tumors were completely removed. The outlook was worse in patients with neurofibromatosis, who comprised about 20% of these patients. Local treatment failure was a more common result than was the development of distant metastases.
6. M. Terrier Lacombe (Villejuif, France) described the various types of malignant fibrous tumors in childhood, including fibrosarcoma, monophasic synovial sarcoma, malignant fibrous histiocytoma, the more recently diagnosed inflammatory fibrosarcoma, and desmoplastic small round cell tumor, which occur in the mesentery or retroperitoneum. These tumors show positive staining for vimentin, keratin, and smooth-muscle actin. Fibrosarcoma in infants under a year of age is usually benign in appearance, with regular nuclei and no abnormal mitoses.
7. D. Sommelet-Olive (Nancy, France) presented data on 24 patients with fibrosarcoma and undifferentiated spindle cell sarcoma. Five patients had the former and 19 had the latter diagnosis. Nineteen of the patients were over 1 year of age, and the median age was 10 years. Complete local control was achieved in 20 patients using various combinations of surgery, chemotherapy, and radiation therapy. Sixteen of these 20 were alive in their first complete remission after chemotherapy with ifosfamide, vincristine, and actinomycin D, with or without radiation therapy. Dr. Sommelet also recommended that for patients older than 5 years of age with fibrosarcoma, those with grade 1 tumors probably do not need chemotherapy after complete excision of the tumor. However, if the grade is higher, chemotherapy should be used, as for RMS, and radiation therapy should be considered if there is residual tumor after surgery.

C. Very Rare Soft-Tissue Sarcomas were the topic of the afternoon session, chaired by Drs. Sommelet and Bruno De Bernardi (Genoa, Italy).

1. M. Morgan (Stuttgart, Germany) presented the results of treatment for leiomyosarcoma, liposarcoma, and unclassified sarcoma. In 23 patients with leiomyosarcoma from the combined German and Italian Co-operative Groups, only 7 had primary sites in the abdomen. Four of six achieved a partial response with chemotherapy using vincristine, actinomycin D, and cyclophosphamide (VAC) plus doxorubicin or VA and ifosfamide (I) plus doxorubicin. In 13 patients with liposarcoma, those with totally removed gross disease did well, but those with visible residual tumors or metastatic sarcoma fared very poorly. The response to chemotherapy was not encouraging. Chemotherapy results were better in patients with unclassified sarcoma, whose tumor tissue was either inadequate to study with multiple immunostains or had suboptimal fixation, making classification impossible.
2. U. Gross-Wieltsch (Stuttgart, Germany) presented the results from the combined German and Italian Studies on 16 patients with malignant fibrous histiocytoma. None had distant metastatic disease at diagnosis. Twelve became disease free; only one of them had the prognostically favorable angiomatoid variant.
3. G. Sotti (Padua, Italy) presented the results in 17 patients with vascular sarcomas from the combined German and Italian series. Four of six patients with gross residual disease had a complete or partial response after chemotherapy with VAI or VAC. The results were best when all the tumor was removed at the time of diagnosis. Radiation therapy should be used for any residual tumor.
4. M. Stevens (Birmingham, England) reviewed the literature on the remaining very rare soft-tissue sarcomas. The *extrarenal malignant rhabdoid* tumors were usually diploid or near diploid. Some of them had a monosomy or smaller deletion of chromosome 22, or a translocation of chromosome 22 and 11 or chromosome 22 and 18. Only 17 of 35 patients from the Intergroup Rhabdomyosarcoma Study (26 patients) and the International Society of Pediatric Oncology (SIOP) studies of malignant mesenchymal tumors (MMT) MMT-84 and MMT-89 (8 patients) with adequate follow-up developed a complete response; over half of these patients had already relapsed and most of them had died. *Epithelioid sarcoma* comprised only 2% of the non-RMS soft-tissue sarcomas in the SIOP experience. They usually occurred on the flexor surface of the upper limb and had a relatively slow evolution, which included multiple skin nodules in some cases. Immunostains showed positivity for vimentin and cytokeratin. In the MMT experience, seven of nine patients were alive. With *alveolar soft-part sarcoma*, the evolution was very slow, but the long-term results were not very good. Of the 12 patients in the MMT studies, only 4 achieved a complete response, although 3 of the 4 were sensitive to chemotherapy.
5. R. Spicer (Bristol, England) reviewed soft-tissue tumors that occur in the neonatal period, which is the first month following birth. He grouped them into five categories. The *first* category includes benign tumors, such as fibromas and xanthogranulomas, which may regress by themselves or may require surgery for removal. The *second* category includes tumors that are also benign but tend to recur, such as aggressive fibromatosis. Tumors in the *third* category can be histologically benign (fibrosarcoma) or malignant (alveolar soft-part sarcoma and synovial sarcoma). This group of patients should be treated surgically and may benefit from chemotherapy. The *fourth* category includes obviously malignant tumors, such as RMS and PNET, which should be treated with surgery and chemotherapy, with or without radiation therapy. The *fifth* category includes malignant tumors whose prognosis is relatively poor, such as malignant peripheral nerve sheath tumors. Here surgery and chemotherapy are used.

D. The last session took place during the next morning and consisted of a round table discussion regarding three topics: treatment aspects such as the roles of surgery, radiation therapy, and chemotherapy; the role of pathologic grading; and finally, considerations for an intergroup study. This part of the meeting was chaired by Drs. Françoise Flamant (Villejuif, France) and Raney.

1. *Treatment*

First, Dr. Spicer reviewed the indications for surgical management of patients with these tumors, including the need to remove all of the primary tumor when possible. For patients whose tumors are insensitive to chemotherapeutic agents and/or irradiation, surgical removal is the primary treatment. A second-look operation may be useful in selected patients, especially when the tumor cannot be removed completely at the time of diagnosis but has been reduced in volume after treatment with chemotherapy, irradiation, or both. Removal of metastases should be considered for selected patients, particularly those in whom there is also an option to treat the metastatic site(s) with irradiation or chemotherapy. The surgeon may be useful in helping the brachytherapist deliver interstitial radiation therapy, or in displacing normal tissue away from a planned radiation treatment field.

Next, R. Marcus (Gainesville, FL) discussed aspects of radiation therapy of non-RMS soft-tissue sarcomas in adults. In adults, chemotherapy generally has less utility than in the more sensitive soft-tissue sarcomas in childhood, and therefore radiation therapy becomes more important in trying to achieve local control. There is controversy about the timing of surgery and radiation therapy in achieving local control; some prefer surgical removal followed by irradiation, and others prefer preoperative radiotherapy. Dr. Marcus also discussed some results of radiation therapy in the two Pediatric Oncology Group (POG) studies of non-RMS soft-tissue sarcomas in children. These were the first groupwide studies of non-RMS soft-tissue sarcomas in children in the United States. POG study 8653 was conducted on children under age 21 with IRS clinical groups I and II (localized, grossly removed) and with initially potentially resectable group III (nonremoved, localized) non-RMS soft-tissue sarcomas. Local irradiation was prescribed for patients with group II and III tumors but was not given to those in group I, because they had no residual disease. The local control rate in 73 of these patients was 89% at 5 years for patients with group I and II tumors (grossly completely removed). The local control rate was 97% for tumors smaller than 5 cm and approximately 80% for larger ones. The survival rate at 4 years was greater than 90% in those with pathologic grade 1 and 2 tumors, but only 49% for those with grade 3 tumors. POG study 8654 was conducted on children with advanced non-RMS soft-tissue sarcomas, including initially unresectable group III localized tumors and those with metastases (group IV). The 4-year disease-free survival rate was only 30% in the patients with gross residual tumors and was zero in those with metastases at diagnosis. Dr. Marcus suggested that hyperfractionated radiation therapy might be considered for a future trial, as well as preoperative radiation therapy.

C. Pratt (Memphis, TN) reviewed data from the St. Jude Children's Research Hospital and also data from the POG studies using chemotherapy protocols comprised of vincristine, actinomycin D, and cyclophosphamide (VAC) plus doxorubicin. The St. Jude experience showed that most children with non-RMS soft-tissue sarcomas underwent grossly complete excision of their localized tumor. The extremities and trunk were the two most common sites of primary tumor. The majority of patients with T1 tumors (those not invading surrounding tissues) survived, but only about half of those with T2 (invasive) tumors survived. Patients with grade 3, highly malignant tumors had a worse outlook for survival than did those with less malignant tumors. Dr. Pratt then stated that POG study 8653 showed no benefit from chemotherapy with VAC and doxorubicin compared with observation after surgical removal of the tumor, with radiation therapy on the residual tumor, if any: 9 of 36 who received chemotherapy relapsed, while 7 of 49 treated without chemotherapy relapsed. The disease-free survival rate was 70%, and the overall survival was 80% in those patients. In POG study 8654 of patients with unresectable group III and metastatic tumors, only 15 of 62 patients had a complete response after treatment with surgery, radiotherapy, and chemotherapy. The addition of dacarbazine did not improve the efficacy of VAC plus doxorubicin chemotherapy. The survival of patients with unresectable group III and metastatic tumors was poor.

2. Pathology and Grading Systems

D. Parham (Memphis, TN) reviewed the grading system used in POG studies 8653 and 8654. Patients were assigned to grade 1, 2, or 3 according to the histologic type of the tumor, the amount of mitoses and necrosis, the degree of nuclear atypia, and the degree of cellularity. In this system, some patients' tumors were automatically categorized in grade 1 or grade 3 because of the histologic diagnosis alone, without weight being given to the numbers of mitoses, amount of necrosis, nuclear atypia, or cellularity. *Grade 1* included the myxoid and well-differentiated tumors, the angiomatoid malignant fibrous histiocytomas, and fibrosarcomas and hemangiopericytomas in children less than 4 years of age at diagnosis. Patients with aggressive fibromatosis were excluded. *Grade 2* included those sarcomas that were not specifically grade 1 or 3, whose mitotic index was less than 5 per 10 high power fields, or with less than 15% necrosis, and without a high degree of nuclear atypia or of cellularity. *Grade 3* included all pleomorphic and round cell sarcomas, alveolar soft-part sarcoma, and other non–grade 1 sarcomas with 5 mitoses or more per 10 high power fields, or greater than 15% necrosis. Overall, the grading system was highly prognostic, but proper histologic diagnosis at the outset was of paramount importance in classifying these tumors into well-defined groups.

I. Leuschner (Kiel, Germany) presented a comparison of the grading systems of Dr. Coindre (Bordeaux, France) and that of the POG 8653 and 8654 studies. The Coindre system was used to grade non-RMS soft-tissue sarcomas in the German Cooperative Studies CWS-81 and CWS-86

for children with soft-tissue sarcoma. The threshold levels for necrosis and mitosis in the Coindre system were higher than those in the POG studies. The Coindre system defines grade 3 as more than 50% necrosis and 20 or more mitoses per 10 high power fields, as compared with the lower figures of more than 15% necrosis and 5 mitoses per 10 high power fields used in the POG system. Both systems were prognostically significant, but the POG system was slightly more predictive of outcome. Dr. Leuschner also presented the possibility of using the proliferative index in addition to counting mitoses as a way to obtain more objective information.

3. *Considerations for Future Studies*

Dr. Sommelet-Olive outlined the multiple problems presented by these tumors, including difficulties with pathologic classification and grading, the difficulty of the limited amount of information regarding efficacy of chemotherapy in patients with non-RMS soft-tissue sarcomas, and the possibility of introducing new biologic criteria, such as ploidy and cytogenetic analysis, for separating patients. She reviewed data on adults treated with chemotherapy, which indicate that doxorubicin and ifosfamide are the most useful agents, with or without dacarbazine or possibly vincristine. But it has been difficult to show a survival improvement in adults given chemotherapy compared with those given local treatments, such as surgery and radiation therapy without chemotherapy. She and the SIOP group endorse the use of chemotherapy for patients who have unresectable tumors and metastases at diagnosis, and for patients whose diagnosis is peripheral neuroectodermal tumor, synovial sarcoma, malignant fibrous histiocytoma, or vascular sarcoma. Chemotherapy is probably less useful for the other types of tumors. In the SIOP MMT-84 and MMT-89 studies, 85% of the 240 registered patients had localized sarcomas. A complete remission was obtained in 85% of these patients. It was achieved by initial complete excision in 24% of the patients. The others underwent a partial excision and then had further treatment. After the initial partial excision, a complete remission was produced by chemotherapy (vincristine, actinomycin D, ifosfamide) alone in 30%, by chemotherapy plus repeat surgical excision in 30%, by chemotherapy plus irradiation in 8%, and by chemotherapy plus irradiation plus a second operation in 8%. Thus only 20% of these patients were exposed to the risk of long-term sequelae due to mutilating surgery and/or radiotherapy to a large volume. The event-free survival rate is 65% at 5 years in both SIOP studies. The overall survival rate of the nonmetastatic patients is 73% at 5 years in MMT-84 and 84% at 3 years in MMT-89. It is only 15% in patients with metastases at diagnosis. In patients with measurable disease, primary chemotherapy produced a response rate of 50%.

Present guidelines of treatment are based on the operability of the tumor (radical, wide, marginal, or intralesional excision); the clinical stage; the primary site; the potential chemosensitivity of these tumors; the age, keeping in mind the low grade of malignancy of some sarcomas (fibrosarcoma and vascular sarcomas in infants); and the potential sequelae of radiotherapy. If possible, primary surgery is undertaken, aiming to achieve a macroscopically complete excision with adequate margins; if this seems unlikely, a trial of chemotherapy is preferred. It seems possible to omit radiotherapy in chemosensitive tumors in spite of a microscopic residue. The SIOP group proposes to use the same drug combinations as in RMS for primary chemotherapy, especially in proven or potentially chemosensitive tumors. The role of adjuvant chemotherapy, unproven in adults, needs to be studied in children according to stage and histologic grade.

Dr. Treuner then presented considerations for an Intergroup Study from the Germany and Italian Co-operative Group perspective. First, patients with synovial sarcoma, EOE sarcoma, peripheral neuroectodermal tumor, and those with undifferentiated and unclassified sarcomas should be treated as for rhabdomyosarcoma. Surgical removal is the primary approach for fibrosarcoma and malignant peripheral nerve-sheath tumors. Patients with malignant fibrous histiocytoma, leiomyosarcoma, liposarcoma, vascular sarcoma, alveolar soft-part sarcoma, and clear cell sarcoma should be stratified, probably by histologic grade. Chemotherapy could then be designed according to the histologic grade of the tumor. Patients with microscopic residual or gross residual tumors would receive radiation therapy, and patients with gross residual tumors would also receive chemotherapy, with surgical removal as an option after demonstration of tumor shrinkage.

SUMMARY

Dr. Raney then summarized the meeting. The nonrhabdomyosarcoma soft tissue sarcomas in children are relatively rare tumors that are quite heterogeneous in histology and biologic behavior. The wide range of biologic behavior includes differences in growth rate, patterns of spread, response to chemotherapy and radiation

therapy, and also differing genetic abnormalities in the tumor tissue. The etiology of these diseases, which is totally unclear at this point, is also likely to be diverse. Treatment should include surgical removal when feasible. Chemotherapy is generally considered somewhat less effective than in patients with rhabdomyosarcoma but has a role in many patients. Non-RMS soft-tissue sarcomas may not be so sensitive to radiation therapy as are rhabdomyosarcomas, and the role of radiation therapy is still evolving. Yet irradiation is still an integral part of the management of patients with non-RMS soft-tissue sarcomas, except when there is no residual tumor following surgical removal of localized disease. Finally, and most importantly, cooperative studies are *essential* to increase the knowledge in all fields relative to these tumors: etiology, biology, diagnosis, and proper management of the patients.

The conference was then closed by Dr. Carli, who thanked all the participants and attendants. All agreed that this was a very worthwhile meeting, whose most important aspect was bringing together pathologists, clinicians, and laboratory scientists to try to understand the behavior of these tumors and to improve the therapeutic results in our patients.